prejudice. Applicant has also amended claims 29 and 30 to remove the dependence from nonelected claim 2 and to correct minor formatting errors. Support for the amendments to claims 29 and 30 can be found in the specification at, *inter alia*, page 29, line 7 to page 30, line 34; page 35, lines 2-7; page 36, line 15 to page 37, line 2; page 37, line 36 to page 38, line 13; and page 42, lines 18-25. Applicant maintains that the amendment of claims 29 and 30 does not raise any issue of new matter. Accordingly, applicant respectfully requests entry of this Amendment. Upon entry of this Amendment, claims 29-34 will be pending and under examination.

Objections to the Specification

The Examiner objected to the abstract of the disclosure because, according to 37 C.F.R. §1.72, the abstract should not exceed 150 words. In response, applicant has hereinabove amended the abstract to reduce its length.

The Examiner also requested that the status of application 09/040,833, disclosed in the first paragraph on page 1 of the specification, be updated. In response, applicant has hereinabove amended the specification to indicate that application 09/040,833 is now issued U.S. Patent No. 6,197,582.

Rejections under 35 U.S.C. §112, First Paragraph

Claim 34

The Examiner rejected claim 34 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner further indicated that the deposit of trioma cell ATCC HB 12482 would satisfy the enablement requirements of 35 U.S.C. §112, first paragraph, and that in addition, the identifying information set forth in 37 C.F.R. §1.809(d) should be added to the specification.

In response, applicant affirms that the above-mentioned trioma cell line was deposited on March 17, 1998, pursuant to the Budapest Treaty, with the Patent Culture Depository of the American Type Culture Collection (ATCC) under ATCC Designation No. HB 12482. For the Examiner's convenience, applicant attaches hereto as **Exhibit E** a copy of the Budapest Treaty Deposit Receipt and Viability Statement for the trioma cell designated MFP-2 (ATCC No. HB 12482), and notes that a copy of this Receipt and Viability Statement had been previously submitted with a Preliminary Amendment filed January 23, 2001. Applicant notes further that the January 23, 2001 Preliminary Amendment also included the identifying information set forth in 37 C.F.R. §1.809(d).

Consistent with the requirements of C.F.R. 1.808, applicant's undersigned attorneys state that the deposit of the trioma cell line was made under the terms of the Budapest Treaty, and that all restrictions on the availability to the public of the material deposited under ATCC No. HB 12482 will be irrevocably removed upon the grant of a patent on this application. Notwithstanding the above remarks, applicant in no way concedes the correctness of the Examiner's remarks which form the basis of

this rejection.

In view of the foregoing, applicant requests that the Examiner withdraw the rejection of claim 34 under 35 U.S.C. §112, first paragraph.

Claims 29-33

The Examiner rejected claims 29-33 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner stated that the specification discloses a single example of a trioma that can be used to produce antibody-secreting tetromas, whereas the claims encompass the use of many different trioma cell lines with the aforementioned functional attribute. The Examiner therefore concluded that the specification does not provide an adequate written description of the claimed invention.

In response to the Examiner's rejection of claims 29-33, applicant respectfully traverses.

Applicant maintains that the Examiner has failed to establish that the written description is inadequate, and maintains that the specification provides an adequate written description for the subject matter claimed. In particular, the specification presents a detailed protocol for generating a trioma cell beginning with fusion of the commercially available human myeloma cell line, RPMI 8226, and mouse myeloma cell line, X63.Ag8.653,

to produce non-antibody-secreting mouse-human heteromyelomas, B6B11 or B6B11-like cells (see the specification at, *inter alia*, page 29, line 7 to page 30, line 34; page 35, lines 2-7; page 36, line 15 to page 37, line 2; page 37, line 36 to page 38, line 13; and page 42, lines 18-25), followed by fusion of the heteromyeloma with human lymphocytes to produce the non-antibody-secreting, trioma fusion partner cell line, MFP-2 (see, *inter alia*, page 30, line 36 to page 33, line 40; page 38, lines 15-38; and page 42, line 27 to page 43, line 15). Applicant asserts that, based on the detailed guidance provided in the specification, one skilled in the art could reproducibly generate numerous different cell lines with functional attributes equivalent to those of MFP-2. The Examiner has failed to cite any reference or set forth any evidence to suggest that the production of such functional trioma lines would require undue experimentation. Absent such a showing, the Examiner has not set forth a basis for properly concluding that the subject matter of rejected claims 29-33 is not adequately described in the specification.

For the above reasons, applicant respectfully requests that the Examiner withdraw the rejection of claims 29-33 under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 29-34 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that claims 29 and 30 are indefinite in that they depend from

nonelected claim 2.

In response, applicant points out that claims 29 and 30, as amended, do not depend from claim 2. Accordingly, applicant respectfully requests that the Examiner withdraw the rejection of claims 29-34 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 29-33 under 35 U.S.C. §103(a) as allegedly unpatentable over Oestberg et al. (U.S. Patent No. 4,634,664).

In response, applicant respectfully traverses, and maintains that the Examiner has failed to establish a *prima facie* case of obviousness of claims 29-33 for the following reasons.

Claim 29 provides a method of producing a monoclonal antibody comprising fusing an antibody-producing lymphoid cell with a trioma cell of the instant claims to form a tetroma cell, and then incubating that tetroma cell under conditions permissive to the production of antibody. Claim 30 provides a method of producing a monoclonal antibody specific for an antigen associated with a condition in a subject, comprising selecting a tetroma cell producing a monoclonal antibody, and comparing the amounts of complex formed between the monoclonal antibody and separate samples from subjects with and without the condition, a greater amount of complex formation for the sample from the subject with the condition indicating that a monoclonal antibody specific for the antigen specific for the condition is produced. Claims 31-33 depend, directly or indirectly, from claim 29.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate with respect to each claim, firstly, that the cited reference teaches or suggests every element of the claim; secondly, that one of ordinary skill in the art would have been motivated to make the invention based on the teachings of the cited reference; and thirdly, that there would have been a reasonable expectation that the claimed invention would succeed.

The Examiner has failed to do this.

According to the Examiner, Oestberg et al. teach xenogeneic hybridoma fusion partners that do not produce antibody and the use of said cells as fusion partners to produce monoclonal antibodies upon fusion with an antibody-producing cell. The Examiner stated that Oestberg et al. teach that the antibody-nonproducing xenogeneic hybridoma fusion partner can be made by fusing a myeloma cell to a human lymphocyte, and further that the myeloma cell used can be a hybrid cell formed from the fusion of two cells. The Examiner acknowledged that Oestberg et al. do not teach a "trioma" cell as defined in the specification of the subject application. He nevertheless concluded that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced the claimed method because Oestberg et al. teach use of hybrid myelomas, and allegedly heteromyelomas (e.g., mouse/human myeloma fused cells as in claim 14), as the fusion partner with a non-antibody-secreting human lymphocyte to form a non-antibody-secreting, trioma fusion partner.

In response, applicant maintains that Oestberg et al. fail to teach all elements of the instant claims. Further, Oestberg et

al. provide neither motivation to make the subject invention nor any expectation of success in making it. Applicant notes that the starting cell lines used by Oestberg et al. to develop a fusion partner were the mouse SP2 myeloma (which itself is a mouse myeloma/mouse lymphocyte hybrid) and human peripheral blood lymphocytes (PBLs) (Oestberg et al., column 2, last paragraph, continued on column 3). After the fusion of these two cell types, an antibody-nonproducing heterohybridoma, SPAZ-4, was produced (Oestberg et al., Example 1). Since one of the cell types used in this fusion was a normal human B-lymphocyte and not a myeloma, Oestberg et al.'s fusion partner cell line is a heterohybridoma, not a heteromyeloma. Accordingly, the trioma fusion partner developed by Oestberg et al. is obtained by fusing a heterohybridoma, not a heteromyeloma, with a human PBL. In the claimed invention, by contrast, the trioma is made by fusing a human myeloma cell and a mouse myeloma cell to form a heteromyeloma cell. It is this heteromyeloma cell – and not the heterohybridoma of Oestberg et al. – which is then fused with a human PBL, splenocyte, or lymph node lymphocyte to form a trioma fusion partner cell. Because this element of the claims, i.e., the use of a heteromyeloma, is not taught in Oestberg et al., the Examiner fails the first part of the three-part test for establishing a *prima facie* case of obviousness.

The Examiner has therefore failed to set forth a *prima facie* case of obviousness, and accordingly, applicant respectfully requests that he reconsider and withdraw the rejection of claims 29-33 under 35 U.S.C. §103(a).

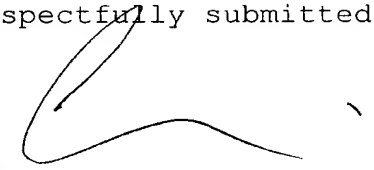
Conclusion

In view of the remarks made herein, applicant respectfully requests that the Examiner withdraw the various grounds of objection and rejection set forth in the January 9, 2003 Office Action, and earnestly solicits allowance of all claims pending in the subject application.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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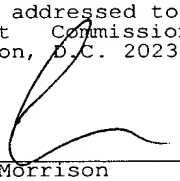

4/5/03
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EXHIBIT A

MARKED-UP VERSION OF AMENDMENT TO SPECIFICATION

Deletions from the text are indicated by square brackets; additions are indicated by underlining.

On page 1, the first paragraph:

> This application is a continuation of U.S. Serial No. 09/040,833, filed March 18, 1998, now [allowed] U.S. Patent No. 6,197,582, the contents of which are hereby incorporated by reference.

EXHIBIT C

MARKED-UP VERSION OF THE ABSTRACT

[The present] This invention provides: a heteromyeloma [cell], other than B6B11, capable of producing a trioma [cell] when fused with a human lymphoid cell, wherein the trioma [cell] is capable of producing a [tetroma cell capable of producing a monoclonal antibody having specific binding affinity for an antigen,] monoclonal antibody-secreting tetroma when fused with a second, antibody-secreting human lymphoid cell; [, the second human lymphoid cell being capable of producing antibody having specific binding affinity for the antigen. The invention provides] a trioma [cell] fusion partner which does not produce [any] antibody, obtained by fusing a heteromyeloma [cell] which does not produce [any] antibody with a human lymphoid cell; [. The invention provides a tetroma cell capable of producing a monoclonal antibody having specific binding affinity for an antigen] a monoclonal antibody-secreting tetroma, obtained by fusing a trioma [cell] which does not produce [any] antibody with [a human lymphoid cell capable of producing antibody having specific binding affinity for the antigen.] an antibody-secreting human lymphoid cell; [The invention provides] a method of producing a monoclonal antibody [specific for] that specifically recognizes an antigen associated with a condition; [The invention provides] a method of identifying an antigen associated with a condition using the trioma fusion partner[.]; [The invention provides] a method of diagnosing a condition using the trioma fusion partner[.]; [The invention provides] a method for preventing a condition[. Compositions]; and compositions and therapeutic compositions [are also provided using] comprising monoclonal antibodies produced using the trioma fusion partner.

EXHIBIT D

MARKED-UP VERSION OF AMENDED CLAIMS

Deletions from the text are indicated by square brackets; additions are indicated by underlining.

29. (Amended) A method of producing a monoclonal antibody comprising:

(a) forming a tetroma cell by fusing a lymphoid cell capable of producing antibody with [the] a trioma cell [of claim 2, thereby forming a tetroma cell; and] which does not produce any antibody, wherein the trioma cell is obtained by fusing a heteromyeloma cell which does not produce any antibody with a human lymphoid cell; and

(b) incubating the tetroma cell formed in step [(b)] (a) under conditions permissive to the production of antibody by the tetroma cell, thereby producing the monoclonal antibody.

30. (Amended) A method of producing a monoclonal antibody specific for an antigen associated with a condition in a subject comprising:

(a) forming a tetroma cell by fusing a lymphoid cell capable of producing antibody with [the] a trioma cell [of claim 2, thereby forming a tetroma cell;] which does not produce any antibody, wherein the trioma cell is obtained by fusing a heteromyeloma cell which does not produce any antibody with a human lymphoid cell;

(b) incubating the tetroma cell formed in step (a) under conditions permissive to the production of antibody by the tetroma cell;

(c) selecting a tetroma cell producing a monoclonal antibody;

(d) separately contacting the monoclonal antibody of step (c) with (1) a sample from a subject with the condition [or], and (2) a sample from a subject without the condition, under conditions permissive to the formation of a complex between the monoclonal antibody and the sample, wherein the sample from the subject with the condition contains the antigen;

(e) detecting the complex formed between the monoclonal antibody and the sample;

(f) determining the amount of complex formed in step (e); and

(g) comparing the amount of complex determined in step (f) for the sample from the subject with the condition with amount determined in step (f) for the sample from the subject without the condition, a greater amount of complex formation for the sample from the subject with the condition indicating that a monoclonal antibody specific for the antigen specific for the condition is produced.

ATCC

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

T : (Name and Address of Depositor or Attorney)

Cooper & Dunham, LLP
Attn: John P. White
1185 Avenue of the Americas
New York, NY 10036

Deposited on Behalf of: The Trustees of Columbia University in the City of New York
(Ref. Docket 55099/JPW/SBS)

Identification Reference by Depositor:	**ATCC Designation**
Human hybridoma fusion partner cell line heteromyeloma B6B11	HB-12481
Human hybridoma fusion partner cell line trioma MFP-2	HB-12482

The deposits were accompanied by: ___ a scientific description _ a proposed taxonomic description indicated above. The deposits were received March 17, 1998 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested April 6, 1998. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Barbara M. Hailey

Barbara M. Hailey, Administrator, Patent Depository

Date: April 6, 1998

cc: Steven B. Stein